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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/520,784

01/10/2005

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EXAMINER

COVINGTON, RAYMOND K

ART UNIT

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1625

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DELIVERY MODE

01/06/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/520,784	Applicant(s) MATSUMOTO ET AL.	
	Examiner Raymond Covington	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 October 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,6,7 and 9-15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,6,7 and 9-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>10/22/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The replacement 1449 of 10/22/07 is included.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 6, 7 and 9-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 it is not clear in the definition of R¹ whether the cycloalkyl definitions of (1) are intended to be ring substituents attached to the moiety via a alkyl as claimed in the other definitions (2), (3) and (4).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6, 7, 9-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of claim 1 where Y is alkyl or alkene, R¹ is alkyl or cyclo alkylphenyl and R² and R³ are, e.g. pyran, morpholine, thiomorpholine and pyridine, does not reasonably provide enablement

for the broader scope of all hydrocarbons, heterocyclic groups. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Scope of 5- to 14-membered heterocyclics having 1 to 4 heteroatoms. . . is not adequately enabled. A review of the specification shows only compounds of formula I where where Y is alkyl or alkene, R¹ is alkyl or cyclo alkylphenyl and R² and R³ are, e.g. pyran, morpholine, thiomorpholine and pyridine, representative of actual working examples.

The limited data provides no clear evaluation of how the remaining scope all hydrocarbon and heterocyclic substituents in any array and degree of unsaturation might affect potency to a large or small degree.

Applicants have failed to establish that the compounds tested are structurally and functionally similar to those tested herein or to known compounds having the same activities.

There is thus no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent . Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush

group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure- sensitive arts such as the pharmaceutical art. Also note the criteria for enablement as set out in *In re Wands* cited in MPEP 2164.01(a), August 2000 edition. Thus given the breadth of the claims, the level of unpredictability in the art and the lack of direction (i.e. working examples) provided as to what other ring systems might work this rejection is applied.

Though clearly one of ordinary skill in the art could identify much of what is within the scope of Y, R¹, R² and R³ the delineation between what is and what is not claimed has not been circumscribed. That is, all of what is claimed is not identifiable. In claim 5, 'heterocyclic is also an optional substituent on hydrocarbon group. The specification only provides some examples of what these terms may signify, but does not limit "heterocyclic" or "hydrocarbon" to any particular definition. For example, pages 12-13 and 15 teach many "particularly preferred" examples of hydrocarbon and heterocyclic groups but this section is prefaced with, may include, so it is clear that applicants do not wish to be limited to only those named. Again, where the delineation between claimed subject matter and unclaimed subject matter lies is unclear from a reading of the claims in light of the specification. More than one definition of the general term "heterocyclic" or "heterocycle" is accepted by those of ordinary skill in the art of organic chemistry.

Some consider cyclic organic compounds wherein at least one carbon atom is replaced by sulfur, oxygen or nitrogen to be heterocyclic compounds, while others of ordinary skill include selenium, tellurium, boron or tin containing rings to be within the scope of the term “heterocyclic” as it is commonly used, and some definitions of “heterocyclic” do not require carbon to be present at all.

The examiner directs applicants' attention to the following three references:

On page 282 of the McGraw--Hill Dictionary of Chemical Terms(1990), the definition of “heterocyclic compound” is a compound in which the ring structure is a combination of more than one kind of atom. On page 490 of the Concise Encyclopedia Chemistry (1993), the definition of “heterocycles” is cyclic hydrocarbon compounds in which the ring consists of carbon and at least one other element, usually, N, O or S. The definition goes on to explain that the possibilities for synthesis are nearly unlimited, and that compounds wherein the heteroatoms are of elements like phosphorous, arsenic, selenium, and tellurium are being incorporated with increasing frequency. On page 594 of Hawley's Condensed Chemical Dictionary (1993), “heterocyclic” is defined as a closed-ring structure, usually, either 5 or 6 members, in which one or more of the atoms in the ring is an element other than carbon, e.g, sulfur, nitrogen, etc. These three definitions should make it abundantly clear that there is no one specific and exact definition of the

word "heterocyclic," thus when this term is present as a claim limitation, the metes and bounds of protection are not pointed out and distinctly claimed. Though the three above-cited definitions of the term have some shared aspects, chemists of ordinary skill would not necessarily agree on the full scope and meaning of the term "heterocyclic."

Applicants' remarks have been noted and considered but are not deemed persuasive of patentability. The 6 examples in the specification, i.e. 57-61 and 65-67 are insufficient to enable compounds of formula (I) embracing all known heterocyclic rings for R¹.

Claims 9-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for having vaniloid receptor agonist activity with example 51 and treating overactive bladder with example 51, it does not reasonably provide enablement for preventing overactive bladder, analgesic or vaniloid receptor agonist activity for all know hydrocarbon and/or all heterocyclic substituted compounds of formula I. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The [eight] factors to be considered [in making an enablement

rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims”, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The main issues are the correlation between clinical efficacy for prevention or treatment and Applicants' assay.

a) Determining if any particular claimed compound would prevent or treat any particular condition would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials and testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large quantity of experimentation. b) The direction concerning preventing or treating is found in pages 3, which merely states Applicants' intention to do so. Applicants describe formulations in pages 41-43. Doses required to practice their invention are described in page 41. A 4-fold range of doses is recommended. Since no one has ever been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? There are no guidelines for determining the doses needed to provide a analgesic effect vs. a overactive bladder preventing effect vs. a anti-inflammation effect. Are the

identical doses to be used for treating these unrelated diseases? There is a cell death expressing assay described in page 206 but it is unclear how this assay is correlated to preventing or treating overactive bladder conditions. c) There is no working example of treatment of any disease in man or animals. The assay provides evidence that the example 51 has receptor activity. However, cell death does not equal treating. d) The nature of the invention is clinical treatment of condition with a compound of the formula I, which involves physiological activity. e) The state of the clinical arts in preventing these conditions is unpredictable.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's

invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). h) The scope of the claims involves all of the thousands of compounds of claim 1. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillard et al EP 0275667 in view of Arya et al US 3954757.

Gillard et al teach benzyindole compounds corresponding to those recited in the claims. See, for example page 4 lines 5-36, page 46 lines 45+ and example 35. Gillard et al differ in that the fused ring is phenyl instead of pyridyl.

However, Arya et al teach analogous bronchitis allergic compounds which show phenyl and pyridyl to be readily interchangeable as the fused ring. See, for example column 1 lines 5-25, column 4 lines 10-20. Note also that carboxyl functional derivative, R₂ definition, reads on the claimed amide-alkyl. In view of the art as a whole to modify Gillard et al would have been obvious to one of ordinary skill in the art as the resulting cumulative effect would not have been unexpected.

Applicants' comments have been noted and considered but are not deemed persuasive of patentability. Regarding Gillard that the substituent CR²CR²-E corresponds to -Y-C(=O)-NR²R³ where E is -C(=O)-NRR. See, for example, page 58 line 44 and the R definitions on page 57. Likewise Arya et al note the "function derivative of a carbonyl group ... containing a nitrogen containing function derivative" column 3 lines 49-54 which also corresponds to these

substituents. The claims drawn to compounds would be expected to have similar properties and uses due to their close structural relationship.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond Covington whose telephone number is (571) 272-0681. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres at telephone number (571) 272-0867.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/R. C./
Examiner, Art Unit 1625

/Janet L. Andres/
Supervisory Patent Examiner,
Art Unit 1625

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